

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

CELERA, AN APPLERA BUSINESS
CORPORATION
Attn: Bansal, Rekha
180 Kimball Way
So. San Francisco, CA 94080
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

Attorney Docket No.:
Date Received:
Action Due:
Docketed

(PCT Rule 44.1)

Date of mailing
(day/month/year)

19/04/2005

Applicant's or agent's file reference

CL001492 PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US2004/041580

International filing date
(day/month/year)

10/12/2004

Applicant

AXYS PHARMACEUTICALS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Natalia Morancho Alcaine

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CL001492 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2004/041580	International filing date (day/month/year) 10/12/2004	(Earliest) Priority Date (day/month/year) 11/12/2003
Applicant AXYS PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

USE OF CATHEPSIN S INHIBITORS FOR TREATING AN IMMUNE RESPONSE CAUSED BY ADMINISTRATION OF A SMALL MOLECULE THERAPEUTIC OR BIOLOGIC

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

International Application No..
PCT/US2004/041580

IPC 7 A61K38/55 A61K31/536 A61P37/06

B. FIELDS SEARCHED

IPC 7 A61P A61K

EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 608 030 B1 (PLOEGH HIDDE L ET AL) 19 August 2003 (2003-08-19)	1,3,5-7, 10,14, 15,17, 19,21, 23,24
Y	column 1, lines 16-23 column 7, lines 30-39,53 column 8, lines 1-10; example 7 ----- -/--	1-25

☒ Patent family members are listed in annex.

'&' document member of the same patent family

19/04/2005

Allnutt, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/041580

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/20485 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC; BEKKALI, YOUNES; HICKEY, EU) 14 March 2002 (2002-03-14) page 2, lines 23-25; claim 1.2 page 246, lines 26-29 page 247, line 31 - page 248, line 4 page 262, lines 42,43 page 263, lines 25,26	1,20,21
Y	-----	1-25
X	WO 03/029200 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC) 10 April 2003 (2003-04-10)	1,20,21
Y	page 179, line 29 - page 181, line 6	1-25
X	RIESE R J ET AL: "CATHEPSIN S ACTIVITY REGULATES ANTIGEN PRESENTATION AND IMMUNITY" June 1998 (1998-06), JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, PAGE(S) 2351-2363 , XP002919128 ISSN: 0021-9738 page 2351, column 1, lines 19,20,24-29 page 2352, column 1, lines 22-30	10,14, 19,22,23
Y	-----	
Y	WO 02/20002 A (ORTHO MCNEIL PHARMACEUTICAL, INC) 14 March 2002 (2002-03-14) page 6, lines 10-19; claim 1	1-25
Y	-----	
Y	SAEGUSA KAORU ET AL: "Cathepsin S inhibitor prevents autoantigen presentation and autoimmunity" JOURNAL OF CLINICAL INVESTIGATION, vol. 110, no. 3, August 2002 (2002-08), pages 361-369, XP002323592 ISSN: 0021-9738 the whole document	1-25
P,X	-----	
P,X	WO 2004/083182 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC; HICKEY, EUGENE, R; LIU, WIE) 30 September 2004 (2004-09-30) page 36, lines 5-7; claim 11; example 5 page 37, lines 1,4,5	1,20,21
P,X	-----	
P,X	WO 2004/028521 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; FOSTER, CAROLYN, ANN; HIESTAND, PET) 8 April 2004 (2004-04-08) claims 1,4	10,11, 19,21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/041580

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-20
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/041580

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6608030	B1	19-08-2003	US 2003166534 A1	04-09-2003
			AT 255126 T	15-12-2003
			AU 723447 B2	24-08-2000
			AU 2741897 A	12-11-1997
			CA 2251714 A1	30-10-1997
			DE 69726426 D1	08-01-2004
			DE 69726426 T2	16-09-2004
			DK 912601 T3	29-03-2004
			EP 1400530 A1	24-03-2004
			EP 0912601 A1	06-05-1999
			ES 2208898 T3	16-06-2004
			JP 2000509376 T	25-07-2000
			NZ 332390 A	28-07-2000
			PT 912601 T	30-04-2004
			WO 9740066 A1	30-10-1997
WO 0220485	A	14-03-2002	US 6420364 B1	16-07-2002
			AU 4569401 A	22-03-2002
			BG 107585 A	28-11-2003
			BR 0113740 A	24-06-2003
			CA 2417177 A1	14-03-2002
			CN 1471511 A	28-01-2004
			CZ 20030603 A3	18-06-2003
			EE 200300093 A	15-02-2005
			EP 1322613 A1	02-07-2003
			HU 0303934 A2	28-04-2004
			JP 2004508356 T	18-03-2004
			MX PA03001947 A	24-06-2003
			NO 20031065 A	07-03-2003
			NZ 525169 A	26-11-2004
			PL 361038 A1	20-09-2004
			SK 2862003 A3	05-08-2003
			US 2002058809 A1	16-05-2002
			WO 0220485 A1	14-03-2002
			US 2003216383 A1	20-11-2003
			US 2004006078 A1	08-01-2004
			US 2003225271 A1	04-12-2003
			US 2003225270 A1	04-12-2003
			US 2003232826 A1	18-12-2003
			US 2002137932 A1	26-09-2002
			US 2005032792 A1	10-02-2005
			US 2005032772 A1	10-02-2005
			ZA 200301032 A	21-04-2004
WO 03029200	A	10-04-2003	CA 2459825 A1	10-04-2003
			EP 1434769 A2	07-07-2004
			JP 2005504827 T	17-02-2005
			WO 03029200 A2	10-04-2003
			US 2004063679 A1	01-04-2004
WO 0220002	A	14-03-2002	AU 8870601 A	22-03-2002
			AU 8871401 A	22-03-2002
			AU 8873001 A	22-03-2002
			AU 8873101 A	22-03-2002
			BR 0114054 A	01-07-2003
			CA 2421493 A1	14-03-2002
			CA 2421502 A1	14-03-2002
			CA 2421505 A1	14-03-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US2004/041580

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0220002	A	CA 2421510 A1	14-03-2002
		CN 1482911 A	17-03-2004
		CN 1473043 A	04-02-2004
		CN 1505509 A	16-06-2004
		CZ 20030635 A3	15-12-2004
		EP 1315490 A2	04-06-2003
		EP 1315741 A2	04-06-2003
		EP 1315491 A2	04-06-2003
		EP 1315492 A2	04-06-2003
		HU 0302475 A2	28-11-2003
		JP 2004523469 T	05-08-2004
		JP 2004531456 T	14-10-2004
		JP 2004508329 T	18-03-2004
		JP 2004508330 T	18-03-2004
		MX PA03001960 A	18-03-2004
		MX PA03001962 A	26-03-2004
		MX PA03001963 A	18-03-2004
		MX PA03001964 A	26-03-2004
		NZ 524680 A	24-09-2004
		NZ 524682 A	26-11-2004
		WO 0220011 A2	14-03-2002
		WO 0220002 A2	14-03-2002
		WO 0220012 A2	14-03-2002
		WO 0220013 A2	14-03-2002
		US 2002115656 A1	22-08-2002
		US 2002035108 A1	21-03-2002
		US 2002147189 A1	10-10-2002
		US 2002055497 A1	09-05-2002
		ZA 200302630 A	05-07-2004
		ZA 200302635 A	15-07-2004
		ZA 200302637 A	05-07-2004
WO 2004083182	A	US 2004180886 A1	16-09-2004
		WO 2004083182 A1	30-09-2004
WO 2004028521	A	AU 2003266404 A1	19-04-2004
		WO 2004028521 A2	08-04-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/041580

International filing date (day/month/year)
10.12.2004

Priority date (day/month/year)
11.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/55, A61K31/536, A61P37/06

Applicant
AXYS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Allnutt, S

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

10/581977

International application No.
PCT/US2004/041580

1AP20 Rec'd PCT/PTO 06 JUN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/041580

Box No. III Non-establishment of opinion with regard to novelty, Inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-20

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,5,13,21,22 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-20 (Industrial Applicability)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/041580

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2,4,8,9,11-13,16,18,25
	No: Claims	1,3,5-7,10,14,15,17,19-24
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	21-25
	No: Claims	1-20

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
 INTERNATIONAL SEARCHING
 AUTHORITY (SEPARATE SHEET)**

PCT/US2004/041580

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
2. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined nor supported.
 The expression "wherein the therapy induces a deleterious immune response" may include for example radiotherapy.
 Support can only be found in the description for an immune response induced by a biologic or small molecule therapeutic.
3. The term "biologic" used in claims 5,13,21 and 22 is considered vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT. For example, is the agent biological in nature or effect.
4. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: US-B1-6 608 030 (PLOEGH HIDDE L ET AL) 19 August 2003 (2003-08-19)
- D2: WO 02/20485 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC; BEKKALI, YOUNES; HICKEY, EU) 14 March 2002 (2002-03-14)
- D3: WO 03/029200 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC) 10 April 2003 (2003-04-10)
- D4: RIESE R J ET AL: "CATHEPSIN S ACTIVITY REGULATES ANTIGEN PRESENTATION AND IMMUNITY" June 1998 (1998-06), JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, PAGE(S) 2351-2363 , XP002919128 ISSN: 0021-9738
- D5: WO 02/20002 A (ORTHO MCNEIL PHARMACEUTICAL, INC) 14 March 2002

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(2002-03-14)

- D6: SAEGUSA KAORU ET AL: "Cathepsin S inhibitor prevents autoantigen presentation and autoimmunity" JOURNAL OF CLINICAL INVESTIGATION, vol. 110, no. 3, August 2002 (2002-08), pages 361-369, XP002323592 ISSN: 0021-9738
- D7: WO 2004/083182 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC; HICKEY, EUGENE, R; LIU, WIE) 30 September 2004 (2004-09-30)
- D8: WO 2004/028521 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; FOSTER, CAROLYN, ANN; Hiestand, PET) 8 April 2004 (2004-04-08)

The documents considered in the present processing are consecutively numbered D1-D8; this numbering results from the citations D1-D8 found in the Search Report (SR) of the corresponding PCT application. It will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

It is noted that the word "may" used in claim 1 also suggests that an immune response may not occur.

Thus claim 1 can be currently understood as a method of administering a cathepsin S inhibitor to a patient undergoing a non-tissue graft therapy.

Novelty

1. The technical features of claims 1,3,5-7,10,14,15,17,19,21,23,24 are disclosed by document D1 and therefore lack novelty in terms of Art 33 (2) PCT.

D1 discloses cathepsin S inhibitors as immunosuppressives through modulation of class II MHC-restricted immune response. The treatment of allergic responses in particularly anaphylactic shock is mentioned. During organ transplantation, the inhibitors can be used in conjunction with antilymphocyte gamma globulin to achieve immunosuppression.

2. The technical features of claims 1,20,21 are disclosed by documents D2 and D3 and

therefore lack novelty in terms of Art 33 (2) PCT.

D2 and D3 discloses Cathepsin S inhibitors for controlling antigen specific immune responses alone and in combination with other active ingredients to overcome adverse side effects.

3. The technical features of claims 10,14,19,22,23 are disclosed by document D4 and therefore lack novelty in terms of Art 33 (2) PCT.

D4 discloses that mice treated with a cathepsin S inhibitor had an attenuated antibody response when immunized with ovalbumin (biologic) and suggests inhibition of cathepsin S is important in modulating the immune response.

4. The remaining claims 2,4,8,9,11-13,16,18 and 25 are considered to be formally novel (Art 33(2) PCT) since their subject matter is not anticipated by prior art documents D1-D6. D5 and D6 discloses the use of cathepsin S inhibitors for disrupting the immune response of allergic reactions and autoimmune disease.

Inventive Step

5. The problem to be solved may be regarded as "how to prevent or overcome an immune response generated by therapeutic agents" (pg 2, l. 14-16).

The solution is the use of cathepsin S inhibitors as defined in claim 20.

However, the present application does not provide any evidence that the posed **problem has been solved** in the form of experimental data. The application only contains suggested studies to carry out the invention without any real data to show a technical effect of the pharmaceutical compounds.

Therefore claims 2,4,8,9,11-13,16,18 and 25, in the absence of evidence that the problem has been solved, cannot be considered as involving an inventive step (Article 33(3) PCT).

Further Remarks:

Industrial Applicability (Art 33(4) PCT).

6. For the assessment of the present claims 1-20 on the question whether they are

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industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Article 64.1 PCT.

7. Although D7 and D8 are not a valid prior art documents pursuant to Art 64.1 PCT, they discloses all the features of claims 1,10,11,19-21.